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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/270,910	03/16/99	IPSEN	H 4305/1E144-U

HM12/1010

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EXAMINER	
HUYNH,P	
ART UNIT	PAPER NUMBER
1644	19

DATE MAILED: 10/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/270,910	IPSEN ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-14,16-34 and 40-50* is/are pending in the application.

4a) Of the above claim(s) *29-31, 40-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-14, 16-28, 32-34 and 47-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 2-14, 16-34 and 40-50 are pending.

2. Claims 29-31 and 40-46 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected inventions.

3. The petition to accept color photographs as drawings under 37 C.F.R. 1.84 (a)(2) and (b)2, filed 8/13/01, is granted. However, Applicants must request amendment of the specification as follows:

Page 1, line 2, insert the following paragraph:

--The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee. --

Furthermore, the Brief Description of the Drawings must be amended to incorporate the color drawing.

4. The following new grounds of objection and rejections are necessitated by the amendment filed 7/20/01.

5. Claims 48 and 50 are objected to because of the following informalities: (1) the phrase "backbone tertiary of the naturally" as recited in claim 48 is missing the word "structure" and (2) The recitation of "(Asn for Thr at position 28, Lys for Gln at position 32, Glu to Ser at position 45, Asn for Ser at position 37, Glu for Ser at position 45, Pro for Gly at position 108 of SEQ ID NO: 37" are recited twice within the claim.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2-14, 32-34, and 47-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a recombinant birch pollen major allergen, Bet v I from the taxonomic order of *Fagales* wherein said recombinant allergen has an amino acid substitution from glutamine to serine at position 45 of the natural Bet v I, and vaspid venom Ves v5, does not reasonably provide enablement for *any* recombinant allergen such as inhalation allergen from the taxonomic order of *Oleales*, *Pinales*, *Asterales*, *Urticales*, allergen from a house dust mite originating from *Dermatophagoides*, cockroach allergen, or animal allergen originating from a cat, dog or horse for a pharmaceutical composition or a vaccine comprising said recombinant allergen against allergic reaction elicited by a naturally occurring allergen in patients suffering from allergy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments filed 7/13/01 have been fully considered but they are not persuasive. Applicants' position is that the specification provides detailed examples of how to make and use two very different source of allergen, i.e., inhalation allergen from birch pollen antigen Bet v1 and vaspid venom Ves v5 and the method of obtaining the mutant allergens as taught in the specification **may be applied** to a wide range of allergen from various source. Applicants further state that it is not necessary to provide *in vivo* data for pharmaceutical compositions and vaccine.

However, the amendment does not overcome the rejection for the reasons stated below.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification discloses only recombinant birch pollen major allergen, Bet v I (SEQ ID NO: 37) from the taxonomic order of *Fagales* wherein said recombinant allergen has an amino acid substitution from Thr to Pro at position 10, from Asp to Gly at position 25, Asn for Thr at position 28, Lys for Gln at position 32, Glu to Ser at position 45, Asn for Ser at position 37, Lys for Asn at position 55, Thr for Ala at position 77, Pro for Gly at position 108 (page 27 of

specification) and vaspid venom Ves v5 having amino acid substitution from Lys to Ala at position 72 and from Tyr to Ala at position 96 of SEQ ID NO: 39 (See pages 44-45).

Besides the specific recombinant birch pollen major allergen Bet v I and vaspid venom Ves v5 mentioned above, the specification fails to provide any guidance as how to make and use recombinant mutant allergen such as inhalation allergen from the taxonomic order of *Oleales*, *Pinales*, *Asterales*, *Urticales*, allergen from a house dust mite originating from *Dermatophagoides*, cockroach allergen, or animal allergen originating from a cat, dog or horse in which at least one surface-exposed amino acid residues of a B cell epitope at a position which is conserved in the amino acid sequences of homologous proteins within the taxonomic order from which the naturally occurring allergen originates is substituted with an amino acid residue which is not conserved in the same position wherein the recombinant mutant allergen has an α-carbon backbone tertiary structure essentially the same as the α-carbon backbone tertiary structure of the naturally occurring allergen and specific IgE binding to the mutant allergen is reduced compared to the IgE binding to the naturally occurring allergen wherein the specific IgE binding to the mutant is reduced by at least 5%, preferably at least 10% wherein at least one patch of conserved amino acid residues comprises atoms of 15-25 amino acid residues ranked with respect to solvent accessibility and one ore more amino acids among the more solvent accessible ones are substituted for a pharmaceutical composition or a vaccine.

There is insufficient guidance as to determine which amino acid residues and the specific type of amino acid within the full-length amino acid sequence of any recombinant allergen mentioned above which can be substitute and whether after amino acid substitutions would maintain the α-carbon backbone tertiary structure and reduced IgE binding at least 5%, or at least 10% as compared to the naturally occurring allergen for a pharmaceutical composition or a vaccine against said allergen. The term "comprises" is open-ended. By reciting the term "comprises" atoms of 15-25 amino acid residues in the claim, the amino acid sequence encompasses indefinite number and type of additional amino acids, in addition to the 15-25 amino acid residues as recited in the claim. It is well known in the art that the relationship between the sequence of a protein and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495).

The state of the prior art as exemplified by Lebecque *et al*, Gajhede *et al* and Elsayed *et al* (all of record) is such that determining the IgE binding of Bet v 1 (B cell epitope) is

conformational dependent by nature, including applicants' disclosure on page 36 bridging to page 37. Given the diversity of B cell epitope ranging from conformational to linear epitope structures, there is no predictability regarding what effect amino acid substitutions will have on the structure and function of all allergen mentioned above because it is difficult to predict the 3-D structure of modified allergens and the resulting binding of IgE *in vivo*. The predictability of making modified allergens mentioned above is limited to factors such as the mutagenesis method. Given the insufficient guidance and working examples, predicting what changes can be made to the amino acid sequence of any allergen mentioned above that after substitution, will retain both structure and reduce IgE function *in vivo* is unpredictable. Since the specification fails to provide guidance regarding which amino acid can tolerate change, it follows that any allergen mentioned above other than Bet v I from the taxonomic order of *Fagales* is not enable.

With regard to a pharmaceutical composition and vaccine comprising said allergen for treating allergy, since IgE-binding properties of any of the recombinant mutant allergen mentioned above have not been demonstrated, it is inconceivable any of the recombinant allergen mentioned above would be useful as a pharmaceutical composition or a vaccine. Even if IgE binding is reduced by 5% or by 10%, there is still a 95% or 90% chance that the mutant allergen will bind IgE. Further, in the absence of in vivo data, is unpredictable for the following reasons: 1) the protein may be inactivated before producing an effect, for instant, due to proteolytic degradation or immunological inactivation as a consequence of the inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment and (4) the route of administration and effective doses have not been demonstrated. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Furthermore, the specification fails to provide guidance as to which part of the α-carbon backbone tertiary structure of the allergen molecule is essentially preserved since the phrase "overall" as recited in claim 2 has been deleted.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 2-14, 16-28, 32-34, and 47-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "**essentially**" in Claims 2 (C) and 48 is indefinite and ambiguous. It is unclear what are the metes and bounds of the term "**essentially**". It is suggested that the term "essentially" be deleted in the claims.

The recitation of "Lys72A or Tyr96A1a" in claim 28 is ambiguous. It is suggested that Applicants amend the claim to recite "from Lys to Ala at position 72 or Tyr to Ala at position 96", for example.

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any

inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

13. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
Oct 9, 2001

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